

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
17 April 2003 (17.04.2003)

PCT

(10) International Publication Number  
**WO 03/030864 A1**

(51) International Patent Classification<sup>7</sup>: **A61K 9/127**,  
31/436, 47/14, C07D 491/22

(21) International Application Number: PCT/US02/16844

(22) International Filing Date: 29 May 2002 (29.05.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
60/294,285 29 May 2001 (29.05.2001) US

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(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,  
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,  
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,  
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,  
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,  
MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI,  
SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU,  
ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM,  
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),  
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),  
European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR,  
GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent  
(BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,  
NE, SN, TD, TG).

**Published:**

— with international search report

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: LIPOSOMAL FORMULATION OF IRINOTECAN

(57) Abstract: The present invention is for novel compositions and methods for treating cancer, particularly, for treating cancer in mammals and more particularly in humans. The therapeutic compositions of the present invention include liposome entrapped irinotecan in which the liposome can contain any of a variety of neutral or charged liposome-forming compounds and cardiolipin. The liposomes of the present invention can be either multilamellar vesicles and unilamellar vesicles, as desired.



**WO 03/030864 A1**

## LIPOSOMAL FORMULATION OF IRINOTECAN

### DESCRIPTION

#### BACKGROUND OF THE INVENTION

5           This invention pertains to formulations and methods for making camptothecin-containing liposomes that minimize or reduce multidrug resistance when administered to humans. The invention is also directed to the use of these liposomes in the treatment of disease, particularly cancer.

#### 10           DESCRIPTION OF THE BACKGROUND

          Camptothecin molecules and irinotecan in particular are potent therapeutic agents for the treatment of cancer. Their metabolite, SN-38, is thought to bind to the enzyme topoisomerase I, the enzyme responsible for relieving torsional strain in DNA. The bound metabolite is thought to be cytotoxic because it blocks religation of the  
15       single-strand breaks induced by topoisomerase-I and thereby disrupts the DNA strands which, are not then sufficiently repaired.

          The metabolic conversion of camptothecins to SN-38 occurs primarily in the liver and is thought to involve carboxylesterase-mediated cleavage of the carbamate bond between the camptothecin moiety and a dipiperidino side chain. Subsequently,  
20       this derivative undergoes conjugation to form the glucuronide metabolite.

          Camptothecins are exceedingly insoluble in aqueous solutions. Despite their lack of solubility in water, they also have a low affinity for lipid membranes from which they tend to precipitate into aqueous phase. These solubility characteristics interfere with their use as therapeutic agents.

25           Irinotecan hydrochloride injection is a first-line therapy for the treatment of patients with metastatic (widespread) colorectal cancer in conjunction with fluorouracil [5FU] and leucovorin. Significant improvements have been observed in objective tumor response rates, time to tumor progression, and prolongation of survival for the regimen of irinotecan hydrochloride and 5FU/leucovorin compared with  
30       5FU/leucovorin alone. Moreover, the addition of irinotecan to the treatment regimen does not interfere with the quality of life of patients. In addition to its current colorectal cancer indication, irinotecan may also find use in adjuvant treatment option (with 5FU/leucovorin) for earlier stage colorectal cancer and for the treatment of other malignancies such as lung and pancreatic cancer.

35           The toxicity inherent in camptothecins limits the dosage of drug that can be administered to patients. For example, certain adverse events such as diarrhea, nausea and vomiting occur more commonly in patients on irinotecan and 5FU/leucovorin than

in patients given 5FU/leucovorin alone. In addition, drug resistance can develop in cells that are repeatedly exposed to the drug. These effects limit the therapeutic effectiveness of camptothecins. Consequently, camptothecin formulations are needed that minimize their toxicity and their toxicity and their tendency to induce cellular multidrug resistance. The present invention provides such a composition and methods. These and other advantages of the present invention, as well as additional inventive features, will be apparent from the description of the invention provided herein.

### SUMMARY OF THE INVENTION

The present invention is for novel camptothecin compositions, including irinotecan compositions, their preparation methods, and their use in treating proliferative diseases such as cancer, particularly in mammals, especially in humans. The compositions of the present invention include liposome-entrapped camptothecin molecules in which the liposome can contain any of a variety of neutral or charged liposome-forming materials and cardiolipin. The liposome-forming material is an amphiphilic molecule such as phosphatidyl choline, cholesterol, dipalmitoyl phosphatidyl choline, phosphatidyl serine, and the like. The cardiolipin in the liposomes can be derived from natural sources or synthetic. Depending on their composition, the liposomes can carry net negative or positive charges or can be neutral. Preferred liposomes also contain  $\alpha$ -tocopherol.

The liposomal compositions can be used advantageously in conjunction with secondary therapeutic agents other than camptothecins, including antineoplastic, antifungal, antibiotic among other active agents, particularly cisplatin, 5-fluorouracil, leucovorin, and their mixtures. The liposomes can be multilamellar vesicles, unilamellar vesicles, or their mixtures as desired. The invention specifically contemplates methods in which a therapeutically effective amount of the inventive liposomes in a pharmaceutically acceptable excipient are administered to a mammal, such as a human.

### DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention provides a composition and method for delivering camptothecins such as irinotecan to a mammalian host. The composition and method are characterized by 1) avoidance of solubility problems, 2) high drug and liposome stability, 3) ability to administer drug as a bolus or short infusion in a high concentration, 4) reduced drug toxicity 5) increased therapeutic efficacy of the drug, and 6) modulation of multidrug resistance in cancer cells.

The inventive composition is a liposome-entrapped camptothecin in which the

liposome also contains cardiolipin. Generally, the liposomes can be formed by known techniques. For example, in one preferred technique irinotecan is dissolved in a hydrophobic solvent with cardiolipin and the cardiolipin allowed to form complexes with irinotecan. The cardiolipin/irinotecan-containing mixture can be evaporated to form a film in order to facilitate complex formation. Thereafter, solutions containing any desired additional lipophilic ingredients can be added to the film and the irinotecan/cardiolipin complexes dissolved or thoroughly dispersed in the solution. The solution can then be evaporated to form a second lipid film. A polar solvent such as an aqueous solvent can then be added to the lipid film and the resulting mixture vigorously homogenized to produce the present inventive liposomes.

Alternatively, all of the lipophilic ingredients can be dissolved in a suitable solvent that can then be evaporated to form a lipophilic film. A polar solvent such as an aqueous solvent can then be added to the lipid film and the resulting mixture vigorously homogenized to produce the present inventive liposomes.

Where the irinotecan is dissolved in the lipid film as described above the dosage form can be conveniently packaged in a single vial to which a suitable aqueous solution can be added to form the liposomes. Alternatively, a two vial system can be prepared in which the lipophilic ingredients are contained as a film in one vial and aqueous ingredients containing irinotecan are provided in a second vial. The aqueous irinotecan-containing ingredients can be transferred to the vial containing the lipid film and the liposomes formed by standard methods.

In a preferred embodiment, the liposomes, once formed, can be filtered through suitable filters to control their size distribution. Suitable filters include those that can be used to obtain the desired size range of liposomes from a filtrate. For example, the liposomes can be formed and thereafter filtered through a 5 micron filter to obtain liposomes having a diameter of about 5 microns or less. Alternatively, 1  $\mu$ m, 500 nm, 100 nm or other filters can be used to obtain liposomes having diameters of about 1  $\mu$ m, 500 nm, 100 nm or any suitable size range, respectively.

In accordance with the invention irinotecan is dissolved in a suitable solvent. Suitable solvents are those in which irinotecan is soluble and which can be evaporated without leaving a pharmaceutically unacceptable residue. For example, non-polar or slightly polar solvents can be used, such as ethanol, methanol, chloroform, or acetone.

Any suitable cardiolipin preparation can be used in the present invention. For example, cardiolipin can be purified from natural sources or can be chemically synthesized, such as tetramyristylcardiolipin, by such methods as are known in the art. Cardiolipin can be dissolved in a suitable solvent as described above for irinotecan and the solutions mixed or the cardiolipin can be dissolved directly with irinotecan.

Any suitable liposome-forming material can be used in the present liposomes. Suitable liposome forming materials include synthetic, semi-synthetic (modified natural) or naturally occurring compounds having a water-soluble, hydrophilic portion and a water-insoluble, hydrophobic portion. Such compounds are amphiphilic molecules and can have net positive, negative, or neutral charges. The hydrophobic portion of liposome forming compounds can include one or more nonpolar, aliphatic chains, for example, palmitoyl groups. Examples of suitable liposome-forming compounds include phospholipids, sterols, fatty acids, and the like. Preferred liposome forming compounds include cardiolipin, phosphatidyl choline, cholesterol, dipalmitoyl phosphatidyl choline, phosphatidyl serine, and  $\alpha$ -tocopherol.

As described above for cardiolipin and irinotecan, the liposome-forming material can be dissolved in a suitable solvent, which can be a low polarity solvent such as chloroform, or a non-polar solvent, such as n-hexane. Other lipophilic ingredients can be admixed with the aforementioned ingredients, the ingredients can then be mixed with irinotecan and the solvent evaporated to produce a homogeneous lipid film. Solvent evaporation can be by any suitable means that preserves the stability of irinotecan and other lipophilic ingredients.

Liposomes can then be formed by adding a polar solution, preferably an aqueous solution, such as a saline solution, to the lipid film and dispersing the film by vigorous mixing. Optionally, the polar solution can contain irinotecan. The solution can be pure water or it can contain salts, buffers, or other soluble active agents. Any method of mixing can be used provided that the chosen method induces sufficient shearing forces between the lipid film and polar solvent to strongly homogenize the mixture and form liposomes. For example, mixing can be by vortexing, magnetic stirring, and/or sonicating. Multilamellar liposomes can be formed simply by vortexing the solution. Where unilamellar liposomes are desired a sonication or filtration step is included in the process.

More generally, any suitable method of forming liposomes can be used so long as it provides liposome entrapped irinotecan. Thus, solvent evaporation methods that do not involve formation of a dry lipid film can be used. For example, liposomes can be prepared by forming an emulsion in an aqueous and organic phase and evaporating the organic solvent. The present invention is intended to encompass liposome-entrapped irinotecan, without regard to the procedure for making the liposomes.

Suitable liposomes can be neutral, negatively, or positively charged, the charge being a function of the charge of the liposome components and pH of the liposome solution. For example, at neutral pH, positively charged liposomes can be formed from a mixture of phosphatidyl choline, cholesterol and stearyl amine. Alternatively,

negatively charged liposomes can be formed from phosphatidyl choline, cholesterol, and phosphatidyl serine.

The preferred liposome entrapped irinotecan composition contains suitable amounts of irinotecan. Suitable amounts can include from 1 to 50 wt.% irinotecan, and more preferably 2 to 25 wt.% irinotecan. Preferred compositions also contain cardiolipin, cholesterol, phosphatidyl choline and  $\alpha$ -tocopherol in suitable amounts. The inventive compositions can contain any suitable amount of cardiolipin. Suitable amounts can include from 1 to 50 wt.% cardiolipin, and more preferably 2 to 25 wt.% cardiolipin. The inventive compositions can contain any suitable amount of phosphatidylcholine. Suitable amounts of phosphatidyl choline can include from 1 to 95 wt.% phosphatidyl choline, and more preferably 20 to 75 wt.% phosphatidyl choline. Preferred liposomes of the present invention also contain suitable amounts of  $\alpha$ -tocopherol or other suitable antioxidants. Suitable amounts range from 0.001 wt.% to 5 wt.%  $\alpha$ -tocopherol. For reference, wt.% refers to the relative mass of each ingredient in the final composition without regard to the amount of added water.

The invention includes pharmaceutical preparations which in addition to non-toxic, inert pharmaceutically suitable excipients contain the liposome-entrapped irinotecan and processes for the production of these preparations.

The invention also includes pharmaceutical preparations in dosage units. This means that the preparations are in the form of individual parts, for example capsules, pills, suppositories and ampoules, of which the content of liposome entrapped irinotecan corresponds to a fraction or a multiple of an individual dose. The dosage units can contain, for example, 1, 2, 3 or 4 individual doses or 1/2, 1/3 or 1/4 of an individual dose. An individual dose preferably contains the amount of irinotecan which is given in one administration and which usually corresponds to a whole, a half or a third or a quarter of a daily dose.

By non-toxic, inert pharmaceutically suitable excipients there are to be understood solid, semi-solid or liquid diluents, fillers and formulation auxiliaries of all kinds.

Tablets, dragees, capsules, pills, granules, suppositories, solutions, suspensions and emulsions, pastes, ointments, gels, creams, lotions, powders and sprays can be suitable pharmaceutical preparations.

Suppositories can contain, in addition to the liposome-entrapped irinotecan, suitable water-soluble or water-insoluble excipients. Suitable excipients are those in which the inventive liposomal entrapped irinotecan are sufficiently stable to allow for therapeutic use, for example polyethylene glycols, certain fats, and esters or mixtures of these substances.

Ointments, pastes, creams and gels can contain suitable excipients in which the liposome-entrapped irinotecan is stable and can contain eucalyptus oil, and sweeteners, for example saccharin.

The irinotecan should preferably be present in the abovementioned  
5 pharmaceutical preparations in a concentration of about 0.1 to 50, preferably of about 0.5 to 25, percent by weight of the total mixture.

The abovementioned pharmaceutical preparations are manufactured in the usual manner according to known methods, for example by mixing the liposome-entrapped irinotecan with the excipient or excipients.

10 The present invention also includes the use of the active compound according to the invention and of pharmaceutical preparations which contain the active compound according to the invention in human and veterinary medicine for the prevention, amelioration and/or cure of diseases, in particular those diseases caused by cellular proliferation, such as cancer, in any mammal, such as a cow, horse, pig, dog or  
15 cat. For example, dog lymphoma can be treated effectively with the present irinotecan formulation. However, the present formulation is particularly preferred for use in the treatment of human patients, particularly for cancer and other diseases caused by cellular proliferation. The inventive compositions have particular use in treating human lymphoma, ovarian, breast, lung and colon cancers.

20 The active compound or its pharmaceutical preparations can be administered locally, orally, parenterally, intraperitoneally and/or rectally, preferably parenterally, especially intravenously.

In a human of about 70 kg body weight, for example, from about 0.5-5.0 mg irinotecan per kg of body weight can be administered. Preferably, about 1.0-3.0 mg of  
25 irinotecan per kg of body weight is administered. However, it can be necessary to deviate from the dosages mentioned and in particular to do so as a function of the nature and body weight of the subject to be treated, the nature and the severity of the illness, the nature of the preparation and if the administration of the medicine, and the time or interval over which the administration takes place. Thus it can suffice in some  
30 cases to manage with less than the abovementioned amount of active compound whilst in other cases the abovementioned amount of active compound must be exceeded. The particular required optimum dosage and the type of administration of the irinotecan can be determined by one skilled in the art, by available methods. Suitable amounts are therapeutically effective amounts that do not have excessive toxicity, as determined  
35 in empirical studies.

One significant advantage of the present composition is that it provides a method of modulating multidrug resistance in cancer cells that are subjected to

irinotecan. In particular, the present liposomal compositions reduce the tendency of cancer cells subjected to chemotherapy with irinotecan to develop resistance thereto, and reduces the tendency of treated cells of developing resistance to other therapeutic agents, such as camptothecin, taxol, or doxorubicin, for example. Thus, other agents  
5 can be advantageously employed with the present treatment either in the form of a combination active with irinotecan or by separate administration. Of course the invention is not intended to be limited to formulations of irinotecan and other interchangeable camptotecin molecules can be used in its place.

10 Having described the present invention it will be apparent that one skilled in the art can make many changes and modifications to the above-described embodiments without departing from the spirit and scope of the present invention.



**WHAT IS CLAIMED IS:**

1. A method of treating a cellular proliferative disease, comprising administering to a mammalian host a pharmaceutical composition comprising:

- 5 (a) a therapeutically effective amount of liposomal entrapped irinotecan also comprising cardiolipin, and  
(b) a pharmaceutically acceptable excipient.

2. The method of claim 1, wherein said mammalian host is a human.

3. The method of claim 1, wherein approximately 3-fold less irinotecan accumulates in cardiac tissue as compared to conventional irinotecan.

4. The method of claim 3, wherein the area under the irinotecan plasma concentration curve is 200-fold higher than with the conventional irinotecan formulation.

5. The method of claim 1, wherein said plasma half life is approximately 10-fold greater than with the conventional irinotecan formulation.

6. The method of claim 1, wherein said cardiolipin is selected from the group consisting of natural cardiolipin and synthetic cardiolipin.

7. The method of claim 1, wherein said liposome bears a negative charge.

8. The method of claim 1, wherein said liposome bears a positive charge.

9. The method of claim 1, wherein at least a portion of said liposome entrapped irinotecan is complexed with cardiolipin.

10. The method of claim 1, wherein said liposomes are a mixture of multilamellar vesicles and unilamellar vesicles.

11. A therapeutic composition comprising a liposome entrapped irinotecan wherein said liposome comprises a first liposome forming material comprising cardiolipin and a second liposome forming material.

12. The composition of claim 11, wherein a portion of said cardiolipin is complexed with irinotecan.

13. The composition of claim 12 wherein said liposome entrapped  
5 irinotecan comprises vesicles having a size of about 5  $\mu\text{m}$  or less.

14. The composition of claim 12 wherein said liposome entrapped irinotecan comprises vesicles having a size of about 1  $\mu\text{m}$  or less.

10 15. The composition of claim 12 wherein liposome entrapped irinotecan comprises vesicles having a size of about 0.5  $\mu\text{m}$  or less.

15 16. The composition of claim 12 wherein said liposome entrapped irinotecan comprises vesicles having a size of about 0.1  $\mu\text{m}$  or less.

17. The composition of claim 11, wherein said second liposome-forming material is a lipid selected from the group consisting of phosphatidyl choline, cholesterol,  $\alpha$ -tocopherol, dipalmitoyl phosphatidyl choline and phosphatidyl serine.

20 18. The composition of claim 11, wherein said cardiolipin is selected from the group consisting of natural cardiolipin and synthetic cardiolipin.

25 19. The composition of claim 11, wherein said liposome bears a negative charge.

20. The composition of claim 11, wherein said liposome bears a positive charge.

30 21. The composition of claim 11, wherein said liposome is neutral.

22. The composition of claim 11, wherein said liposome is a mixture of multilamellar vesicles and unilamellar vesicles.

35 23. A method for the treatment of mammalian cancer comprising administering a therapeutically effective amount of the composition of claim 11 to a subject in need thereof.

24. A method of treating a cellular proliferative disease, comprising administering to a mammalian host a pharmaceutical composition comprising:

(a) a therapeutically effective amount of liposomal entrapped camptothecin also comprising cardiolipin, and

5 (b) a pharmaceutically acceptable excipient.

25. The method of claim 24, wherein said mammalian host is a human.

26. The method of claim 24, wherein approximately 3-fold less  
10 camptothecin accumulates in cardiac tissue as compared to conventional camptothecin.

27. The method of claim 26, wherein the area under the camptothecin plasma concentration curve is 200-fold higher than with the conventional camptothecin formulation.  
15

28. The method of claim 24, wherein said plasma half life is approximately 10-fold greater than with the conventional camptothecin formulation.

29. The method of claim 24, wherein said cardiolipin is selected from the  
20 group consisting of natural cardiolipin and synthetic cardiolipin.

30. The method of claim 24, wherein said liposome bears a negative charge.

31. The method of claim 24, wherein said liposome bears a positive charge.  
25

32. The method of claim 24, wherein at least a portion of said liposome entrapped camptothecin is complexed with cardiolipin.

33. The method of claim 24, wherein said liposomes are a mixture of  
30 multilamellar vesicles and unilamellar vesicles.

34. A therapeutic composition comprising a liposome entrapped camptothecin wherein said liposome comprises a first liposome forming material comprising cardiolipin and a second liposome forming material.  
35

35. The composition of claim 34, wherein a portion of said cardiolipin is complexed with camptothecin.

36. The composition of claim 35 wherein said liposome entrapped camptothecin comprises vesicles having a size of about 5  $\mu\text{m}$  or less.

5 37. The composition of claim 35 wherein said liposome entrapped camptothecin comprises vesicles having a size of about 1  $\mu\text{m}$  or less.

38. The composition of claim 35 wherein liposome entrapped camptothecin comprises vesicles having a size of about 0.5  $\mu\text{m}$  or less.

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39. The composition of claim 35 wherein said liposome entrapped camptothecin comprises vesicles having a size of about 0.1  $\mu\text{m}$  or less.

15 40. The composition of claim 34, wherein said second liposome-forming material is a lipid selected from the group consisting of phosphatidyl choline, cholesterol,  $\alpha$ -tocopherol, dipalmitoyl phosphatidyl choline and phosphatidyl serine.

41. The composition of claim 34, wherein said cardiolipin is selected from the group consisting of natural cardiolipin and synthetic cardiolipin.

20

42. The composition of claim 34, wherein said liposome bears a negative charge.

25 43. The composition of claim 34, wherein said liposome bears a positive charge.

44. The composition of claim 34, wherein said liposome is neutral.

30 45. The composition of claim 34, wherein said liposome is a mixture of multilamellar vesicles and unilamellar vesicles.

46. A method for the treatment of mammalian cancer comprising administering a therapeutically effective amount of the composition of claim 11 to a subject in need thereof.

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## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/16844

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(7) : A61K 9/127, 31/436, 47/14; C07D 491/22

US CL : 424/450; 514/283, 786; 546/48

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/450; 514/283, 786; 546/48

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
Please See Continuation Sheet**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,834,012 A (PEREZ-SOLER ET AL) 10 November 1998 (10.11.98), see entire document, especially Table 1, column 11, line 61 - column 12, line 7.	1-46
X	US 6,214,388 B1 (BENZ ET AL) 10 April 2001 (10.04.01), see entire document, especially column 10, lines 12-36, column 16, lines 42-44.	1-46
X	WO 95/08986 A1 (SMITHKLINE BEECHAM CORPORATION) 06 April 1995 (06.04.95), see entire document, especially the Abstract, page 5, lines 14-17, page 6, lines 26-27 and 33-35, and claims 1, 9, and 27.	24-46
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Y		1-23
Y	Y. SADZUKA, Effective Prodrug Liposome and Conversion to Active Metabolite. Current Drug Metabolism. 2000, Volume 1, Number 1, pages 31-48, see entire document, especially the Abstract.	1-23
Y	SADZUKA et al., Effect of liposomalization on the antitumor activity, side-effects and tissue distribution of CPT-11. Cancer Letters. 1998, Volume 127, pages 99-106, see entire document, especially the Abstract.	1-23



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	
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Date of the actual completion of the international search

16 July 2002 (16.07.2002)

Date of mailing of the international search report

05 SEP 2002

Name and mailing address of the ISA/US  
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# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/16844

## Continuation of B. FIELDS SEARCHED Item 3:

EAST, DIALOG

search terms: irinotecan, camptothecin, liposome, vesicle, diphosphatidylglyceride, cardiolipin